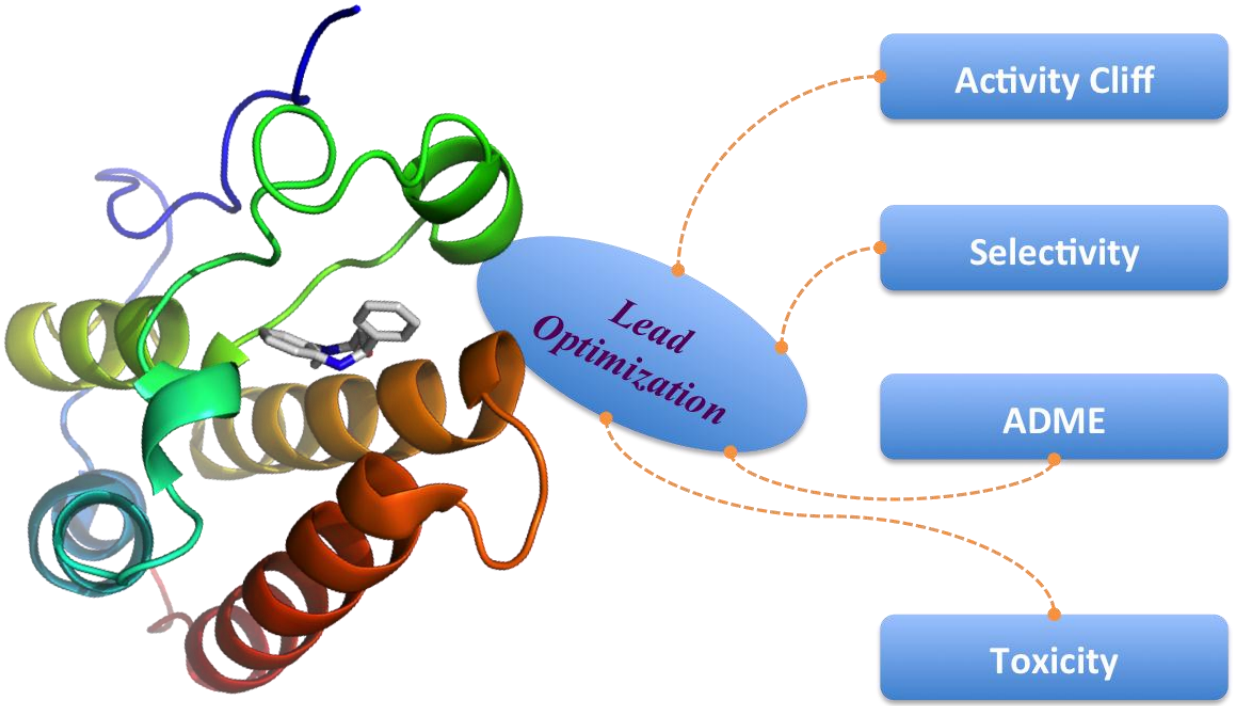


Drug Design

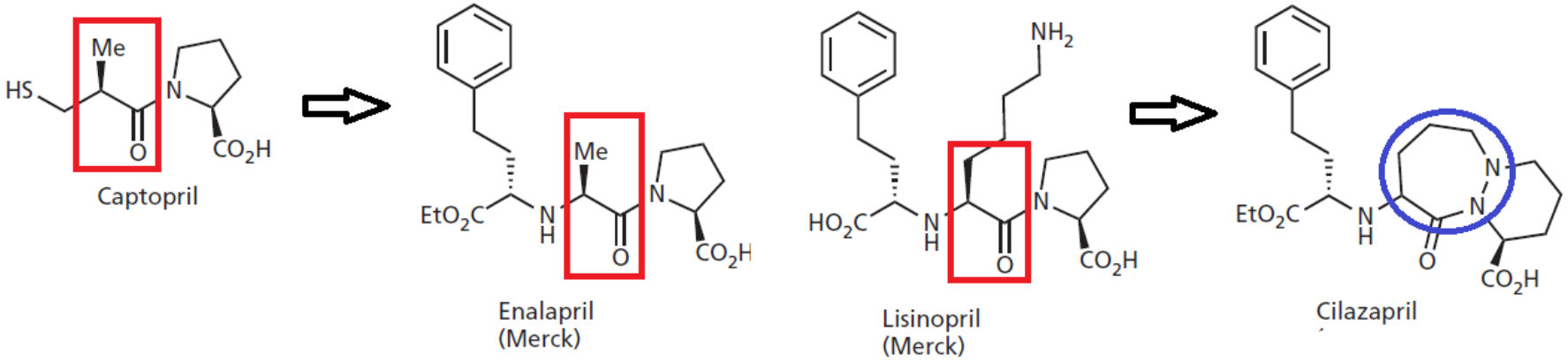
by

Dr. Ashraf Kareem El-Damasy

3.7- Rigidification of the structure (Locking a rotatable bond)

- Imposition of some degree of molecular rigidity into a flexible molecule (by incorporation of the elements of the flexible molecule into a rigid ring system OR by introducing a C=C or C ≡ C) may result in potent agents with highly specific pharmacological effect and reduced side (undesirable) effects.

- Ex.1: Development of the anti-hypertensive agent cilazapril from captopril



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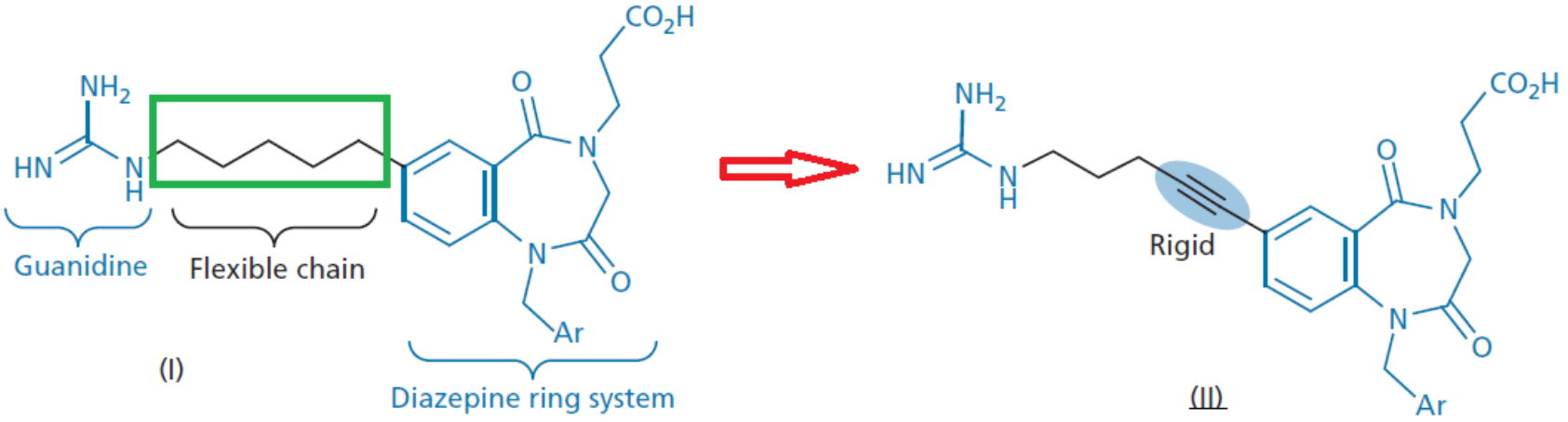
- Ex.1: Investigation of diazepine (I) as a platelet aggregation inhibitor

(Locking the rotatable bond by alkyne introduction)



3.8- Isosteric and Bioisosteric substitution

Definition of Isosterism

- Langmuir (1919): Compounds or groups of atoms having the same number of atoms and electrons.
- Examples: N_2 and CO, N_2O and CO_2, N_3^- and NCO^-
- Grimm (1925): "Hydride Displacement Law" addition of hydride to an atom gives to the resulting pseudoatom' the properties of the atom with the next highest atomic number.

Hydride Displacement Law					
C	N	O	F	Ne	Na^+
	CH	NH	OH	FH	-
		CH_2	NH_2	OH_2	FH_2^+
			CH_3	NH_3	OH_3^+
				CH_4	NH_4^+

- Erlenmeyer (1932): atoms, ions or molecules in which the peripheral layers of electrons can be consider identical.

  Examples: atoms in the same column of the periodic table, Cl and CN and SCN (despite having different number of atoms).

3.8- Isosteric and Bioisosteric substitution

Definition of Bioisosterism

- Friedman (1951): Bioisosteres are atoms or molecules that fit the broadest definition for isosteres and have the same type of biological activity.
- Thornber (1979): Groups or molecules which have chemical and physical similarities producing broadly similar biological effects.

classical bioisostere

Classical bioisosteres represent the results of an early appreciation of the concept and encompass structurally simple atoms or groups.

1) monovalent atoms or groups

D and H
F and H
NH_2 and OH
RSH and ROH
F, OH, NH_2 and CH_3
Cl, Br, SH and OH

2) divalent atoms or groups

C=C, C=N, C=O, C=S
$-CH_2-$, –NH–, –O–, –S–

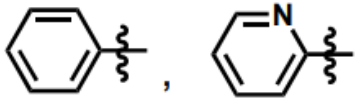
3) trivalent atoms or groups

–CH=, –N=

4) tetrasubstituted atoms

R_4C, R_4Si, R_4N^+

5) ring equivalent



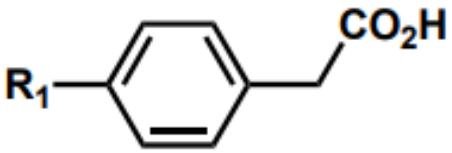
3.8- Isosteric and Bioisosteric substitution

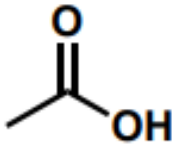
nonclassical bioisostere

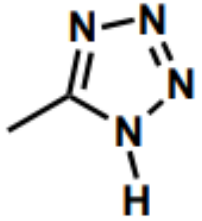
Nonclassical bioisosteres are structually distinct, usually comprise different number of atoms and exhibit different steric and electronic properties.

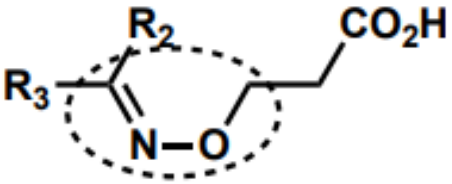
Nonclassical bioisosteres have been devided into two subgroups.

1) cyclic and noncyclic isosteres
2) exchangeable group isosterism in which the properties of discrete functional elements are emulated

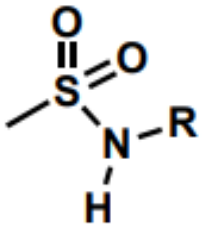








MAOMM
(methyleneaminoxy)-methyl moiety



Carboxylic Acid Isosteres

3.8- Isosteric and Bioisosteric substitution

Parameters affected with bioisosteric replacements

Isosteres are usually in drug design to vary the character of the molecule in a rational way with respect to features such as :

Size, conformation, inductive and mesomeric effects, polarizability, H-bond formation capacity, pKa, solubility, hydrophobicity, reactivity, stability.

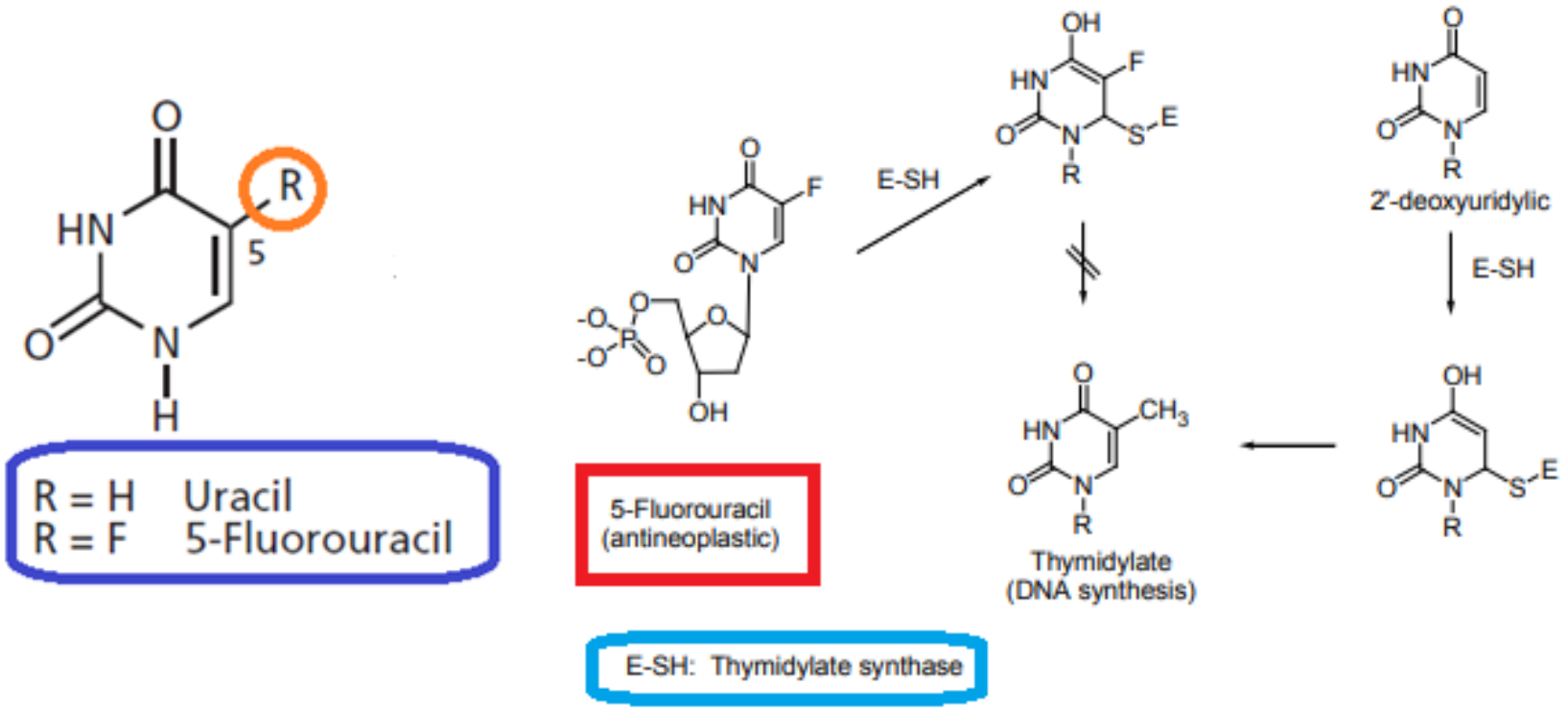
Objectives of Bioisosteric replacements:

- ✓ Improving potency
- ✓ Enhancing selectivity
- ✓ Altering physical properties
- ✓ Reducing or redirecting metabolism
- ✓ Eliminating or modifying toxicophores
- ✓ Acquiring novel intellectual property

3.8- Isosteric and Bioisosteric substitution

Ex. 5-Fluorouracil as antimetabolite (thymidylate synthase inhibitor).

- ✓ **5-FU is converted in vivo into 5-FdUMP which inhibits thymidylate synthase *via* covalent bond formation.**
- ✓ **The presence of F instead of an enzymatically labile H disrupts the enzymatic reaction, as C–F bonds are not easily broken.**



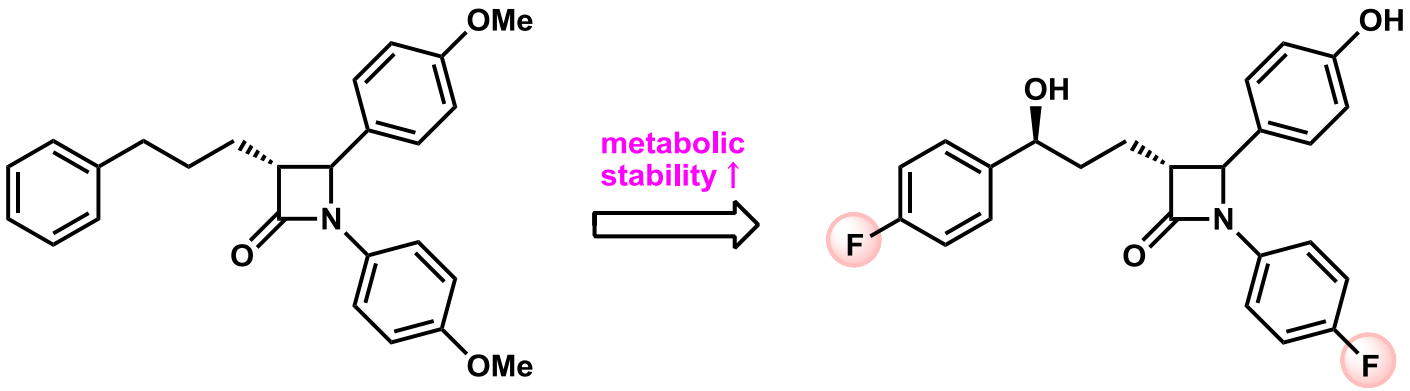
Fluorine as an Isostere of Hydrogen

- The unique properties of fluorine have led to its widespread application in drug design as an isostere for hydrogen,

Ex: Improvement of metabolic stability

- Blocking the metabolically labile site with a fluorine substituent, hoping that the small fluorine atom will not impair the binding to the target protein.

Cholesterol absorption inhibitor (Hyperlipidemia)



Lead compound

ED_{50} (hamster) = 2.2 mg/kg

Ezetimib

ED_{50} (hamster) = 0.04 mg/kg

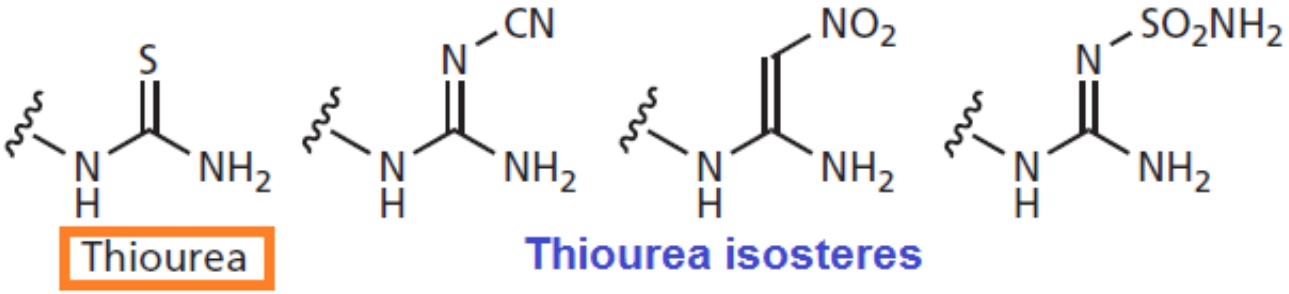
3.8- Isosteric and Bioisosteric substitution

- Bioisosteres are commonly used in drug design to replace a problematic group while retaining activity.

1) The use of a bioisostere can lead to reduced side effects

Ex.1: Thiourea bioisosteres

The thiourea group was present as important binding group in early histamine antagonists, but was responsible for toxic side effects. Replacing it with bioisosteres retained the important binding interactions for histamine antagonism but avoided the toxicity problems.



3.8- Isosteric and Bioisosteric substitution

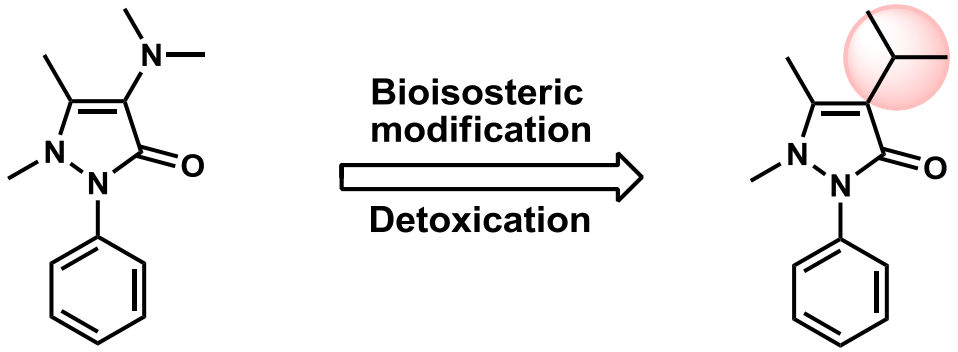
- Bioisosteres are commonly used in drug design to replace a problematic group while retaining activity.

2) The use of a bioisostere can eliminate drug's toxicity

Ex.2: Development of Propylphenazone

✓Aminopyrine was marketed as an analgesic and anti-inflammatory drug in 1896. In 1922, It was revealed that Aminopyrine was a carcinogen!

✓Propylphenazone: Developed by Roche in 1951. Bioisosteric modification of dimethylamino group removed its carcinogenic action.



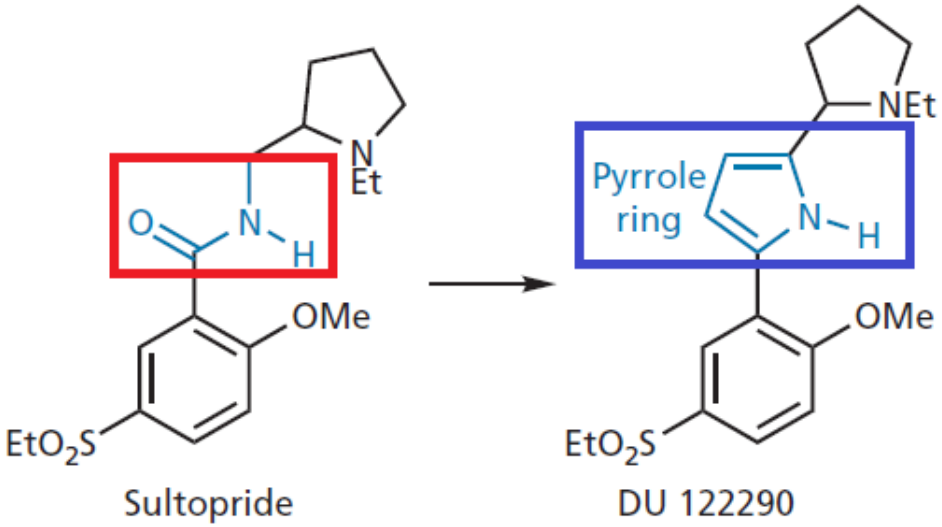
Aminopyrine **Propylphenazone**

3.8- Isosteric and Bioisosteric substitution

3) The use of a bioisostere can increase target interactions and/or selectivity

Ex.3: DU 122290 from Sultopride

A pyrrole ring has frequently been used as a bioisostere for an amide. Such replacement on sultopride (dopamine antagonist antipsychotic) led to *increased activity and selectivity* towards the dopamine D3-receptor over the dopamine D2-receptor).

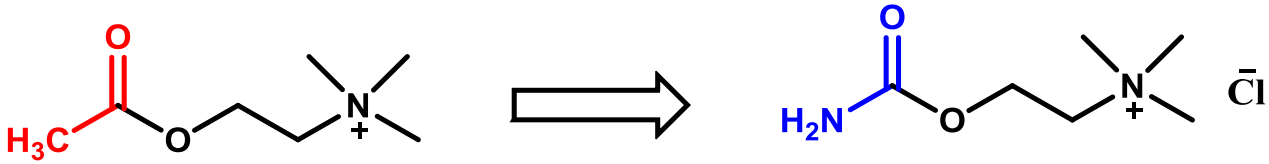


3.8- Isosteric and Bioisosteric substitution

5) The use of a bioisostere can improve the drug's stability

Ex.5: Development of Carbachol

- ✓ Replacing the Me group of an ethanoate ester with NH_2 increases the drug's stability.
- ✓ The NH_2 group is the same valency and size as the Me group and, therefore, has no steric effect, but it has totally different electronic properties (it can feed electrons into the carboxyl group and making it less electrophilic) and stabilize it from hydrolysis.



Acetylcholine

Carbachol

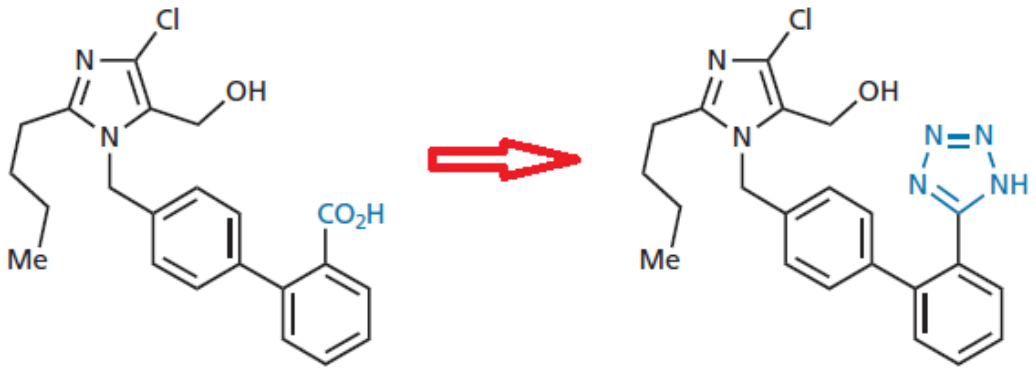
3.8- Isosteric and Bioisosteric substitution

4) The use of a bioisostere can increase oral absorption

Ex.4: Development of losartan

Structure I has poor oral absorption because of the polar –COOH group. Isosteric replacement of -COOH with 5-substituted tetrazole ring (10 times more lipophilic than -COOH) can improve the drug absorption.

- ✓ Tetrazoles resemble -COOH in being: Acidic, planar
- ✓ In addition, metabolically more stable and more lipophilic.



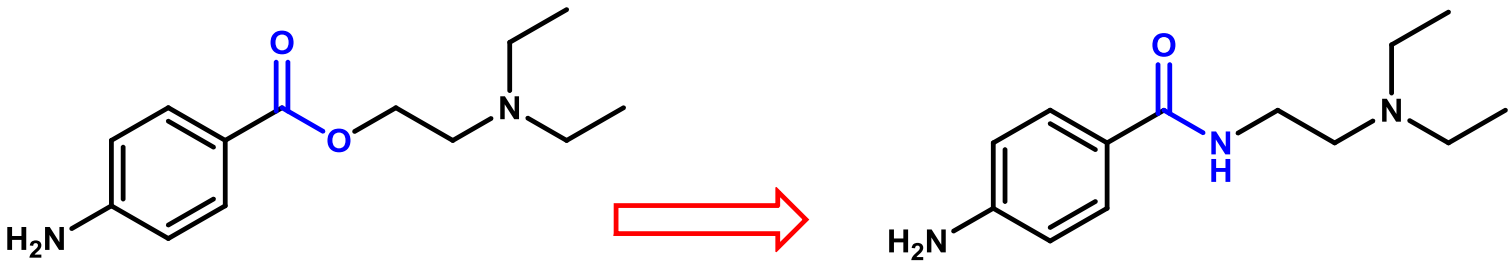
Structure I Losartan

3.8- Isosteric and Bioisosteric substitution

5) The use of a bioisostere can improve the drug's stability and change the biological activity!!!

Ex.6: Development of Procainamide

- ✓ Replacing the ester group of procaine amide led to procainamide with increased drug stability.
- ✓ Relatively, the amide group is metabolically more than ester.



Procaine

Procainamide